

10



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
 United States Patent and Trademark Office  
 Address: COMMISSIONER FOR PATENTS  
 P.O. Box 1450  
 Alexandria, Virginia 22313-1450  
 www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/627,206	07/27/2000	Jane A. Gross	98-75C2	1238

7590 08/06/2004

Phillip B C Jones J D Ph D  
 ZymoGenetics Inc  
 1201 Eastlake Avenue East  
 Seattle, WA 98102

EXAMINER

ZEMAN, ROBERT A

ART UNIT	PAPER NUMBER
----------	--------------

1645

DATE MAILED: 08/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/627,206

Applicant(s)

GROSS, JANE A.

Examiner

Robert A. Zeman

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 27 May 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 89 and 102-111 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 89 and 102-111 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

Art Unit: 1645

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 5-27-04 has been entered. It should be noted that Applicant requested that the amendment filed on 10-27-~~2004~~ be entered. It is assumed that applicant was referring to the amendment filed on 10-30-2003. Moreover, said amendment was entered prior to the Advisory Action mailed on 3-9-2004.

Claims 89 and 102-111 are pending and currently under examination.

### ***Claim Rejections Maintained and New Grounds of Rejection***

#### ***35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Art Unit: 1645

The instant claims are drawn to methods of inhibiting B cell proliferation by the administration of a soluble form a ztnf4 receptor (TACI) wherein said receptor binds ztnf4. Said soluble form of the ztnf4 receptor can comprise the extracellular domain of the TACI protein and may be optionally fused to the heavy chain constant region of human immunoglobulins. Additionally, said soluble form of the ztnf4 receptor may comprise multiple polypeptide fusions.

Claims 89, 102-103, 105-108 and 110-111 are rejected under 35 U.S.C. 102(a) as being anticipated by Bram et al. (WO 98/39361 – IDS-5) for the reasons set forth in the previous Office action in the rejection of 89, 102 and 107.

**Applicant argues:**

1. The pending claims are not to a composition but to methods of use, specifically, methods of inhibiting B lymphocyte proliferation in a mammal.
2. The inhibition of B cell proliferation and binding characteristics of ztnf4 cannot be disclosed in the Bram et al. reference as neither the existence of the ztnf4 protein nor the ligand receptor relationship between ztnf4 and TACI were known at the time of the publication of this information.
3. Only through impermissible hindsight reconstruction could the presently claimed method of inhibiting B cell proliferation be characterized as anticipated.
4. The Examiner appears to be stating that the presently claimed method of inhibiting B cell proliferation is inherently disclosed in the Bram et al. reference.
5. Disclosure of the receptor does not inherently disclose the identity of its ligand or that ligand's activity especially when the identity of that ligand is unknown.

Art Unit: 1645

6. The standard for the determination of inherent teachings requires that the assertedly anticipating disclosure enabled the subject matter of the reference and thus that of the patented invention without undue experimentation.
7. The conclusion of undue experimentation in the instant case is supported by the significant amount of experimentation that would be required in addition to the Bram et al. teachings to reach the present method.

Applicant's arguments have been fully considered and deemed non-persuasive.

Ztnf4 is a member of the tumor necrosis factor (TNF) superfamily. Ztnf4 stimulates proliferation of, and immunoglobulin production by, B cells. Moreover, Ztnf4 is a ligand for TACI and is also known in the art as BLYS, neutrokin  $\alpha$ , BAFF, TALL-1 and THANK.

Bram et al. disclose methods of using genetically engineered constructs to regulate B-cell activity through its interaction with cellular receptor ligands. Said constructs can consist of the extracellular domain of the TACI receptor fused to the Fc domain of an immunoglobulin (see page 24, lines 24-26). Moreover, Bram et al. disclose that the "subunits" of the construct (i.e. TACI and the Fc domain of the Ig) can be linked by peptide bonds (see page 20, line 1). Bram et al. further disclose that said extracellular domain has the amino acid sequence corresponding to about residue 1 to about residue 166 of the consensus sequence of TACI and that the ligand binding region is a sub-fragment of the extracellular domain (see page 18, lines 27-30). Said constructs (fusion proteins) intercept the normal endogenous ligands (i.e. ztnf4) that serve to cross-link and activate the TACI proteins on the surface of cells thus inhibiting the ligand's activity (see page 8, lines 1-6). Consequently, by utilizing the methods and materials disclosed by Bram et al., one would necessarily inhibit the activity of ztnf4, even though its

Art Unit: 1645

identity is not known, since ztnf4 is an **endogenous ligand of TACI**. One does not need to know the identity of the TACI ligand in order to practice the method disclosed by Bram et al. Hence, Applicant's argument that the identification of the ztnf4 ligand would require undue experimentation is not germane. The instant claims only require that the TACI fusion protein be administered to an individual in order to inhibit B cell proliferation and that said composition binds ztnf4. Bram et al. disclose the administration of the same the compositions for the expressed purpose of inhibiting B cell proliferation (which is a ztnf4 activity). Moreover, since the fusion proteins disclosed by Bram et al. are identical to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention (including the ability to bind the ztnf4 ligand).

It should be noted that Applicant's argument that only through impermissible hindsight reconstruction could the presently claimed method of inhibiting B cell proliferation be characterized as anticipated is not germane to rejections made under 35 U.S.C. 102 but to those made under 35 U.S.C. 103.

Additionally Applicant is reminded "the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Finally, with regard to the limitation "proteins comprising one or more polypeptide fusions" recited in claims 105-106 and 110-111, Bram et al. anticipates this limitation since their disclosed fusion protein comprise one polypeptide fusion (i.e. the TACI-Fc fusion protein constitutes a single polypeptide fusion).

Consequently, for the reasons set forth above, Bram et al. anticipates all the limitations of the rejected claims.

Art Unit: 1645

Claims 89, 102-103, 105-108 and 110-111 are rejected under 35 U.S.C. 102(e) as being anticipated by Bram et al. (U.S. Patent 5,969,102 – IDS-5) for the reasons set forth in the previous Office action in the rejection of 89, 102 and 107.

**Applicant argues:**

1. The pending claims are not to a composition but to methods of use, specifically, methods of inhibiting B lymphocyte proliferation in a mammal.
2. The inhibition of B cell proliferation and binding characteristics of ztnf4 cannot be disclosed in the Bram et al. reference as neither the existence of the ztnf4 protein nor the ligand receptor relationship between ztnf4 and TACI were known at the time of the publication of this information.
3. Only through impermissible hindsight reconstruction could the presently claimed method of inhibiting B cell proliferation be characterized as anticipated.
4. The Examiner appears to be stating that the presently claimed method of inhibiting B cell proliferation is inherently disclosed in the Bram et al. reference.
5. Disclosure of the receptor does not inherently disclose the identity of its ligand or that ligand's activity especially when the identity of that ligand is unknown.
6. The standard for the determination of inherent teachings requires that the assertedly anticipating disclosure enabled the subject matter of the reference and thus that of the patented invention without undue experimentation.
7. The conclusion of undue experimentation in the instant case is supported by the significant amount of experimentation that would be required in addition to the Bram et al. teachings to reach the present method.

Art Unit: 1645

Applicant's arguments have been fully considered and deemed non-persuasive.

Ztnf4 is a member of the tumor necrosis factor (TNF) superfamily. Ztnf4 stimulates proliferation of, and immunoglobulin production by, B cells. Moreover, Ztnf4 is a ligand for TACI and is also known in the art as BLyS, neutrokin  $\alpha$ , BAFF, TALL-1 and THANK.

Bram et al. disclose methods of using genetically engineered constructs to regulate B-cell activity through its interaction with cellular receptor ligands. Said constructs can consist of the extracellular domain of the TACI receptor fused to the Fc domain of an immunoglobulin (see column 17, lines 16-18). Moreover, Bram et al. disclose that the "subunits" of the construct (i.e. TACI and the Fc domain of the Ig) can be linked by peptide bonds (see column 13, line 64). Bram et al. further disclose that said extracellular domain has the amino acid sequence corresponding to about residue 1 to about residue 166 of the consensus sequence of TACI and that the ligand binding region is a sub-fragment of the extracellular domain (see column 13, lines 7-12). Said constructs (fusion proteins) intercept the normal endogenous ligands (i.e. ztnf4) that serve to cross-link and activate the TACI proteins on the surface of cells thus inhibiting the ligand's activity (see column 5 lines 45-53). Consequently, by utilizing the methods and materials disclosed by Bram et al., one would necessarily inhibit the activity of ztnf4, even though its identity is not known, since ztnf4 is an **endogenous ligand of TACI**. One does not need to know the identity of the TACI ligand in order to practice the method disclosed by Bram et al. Hence, Applicant's argument that the identification of the ztnf4 ligand would require undue experimentation is not germane. The instant claims only require that the TACI fusion protein be administered to an individual in order to inhibit B cell proliferation and that said composition binds ztnf4. Bram et al. disclose the administration of the same the compositions for the expressed purpose of inhibiting B cell



Art Unit: 1645

proliferation (which is a ztnf4 activity). Moreover, since the fusion proteins disclosed by Bram et al. are identical to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention (including the ability to bind the ztnf4 ligand).

It should be noted that Applicant's argument that only through impermissible hindsight reconstruction could the presently claimed method of inhibiting B cell proliferation be characterized as anticipated is not germane to rejections made under 35 U.S.C. 102 but to those made under 35 U.S.C. 103.

Additionally Applicant is reminded "the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Finally, with regard to the limitation "proteins comprising one or more polypeptide fusions" recited in claims 105-106 and 110-111, Bram et al. anticipates this limitation since their disclosed fusion protein comprise one polypeptide fusion (i.e. the TACI-Fc fusion protein constitutes a single polypeptide fusion).

Consequently, for the reasons set forth above, Bram et al. anticipates all the limitations of the rejected claims.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant claims are drawn to methods of inhibiting B cell proliferation by the administration of a soluble form of a ztnf4 receptor (TACI). Said soluble form of the ztnf4 receptor can comprise the extracellular domain of the TACI protein that is optionally fused to the heavy chain constant region of human immunoglobulins. Additionally, said soluble form of the ztnf4 receptor may comprise multiple polypeptide fusions.

The rejection of claims 89 and 102-111 under 35 U.S.C. 103(a) as being unpatentable over Bram et al. (WO 98/39361 – IDS-5), as cited above, in view of Presta et al. (U.S. Patent 5,739,277) is maintained for reasons of record.

**Applicant argues:**

1. Bram et al. do not teach the BLyS protein, its activities or the ability of TACI and BLyS to bind (see above).
2. The disclosure by Presta et al. is insufficient to overcome the aforementioned deficiency.

Art Unit: 1645

3. Since the combination of references fails to teach all the limitations of the instant invention, their combined teachings does not render the presently claimed invention obvious.

Applicant's arguments have been fully considered and deemed non-persuasive.

Ztnf4 is a member of the tumor necrosis factor (TNF) superfamily. Ztnf4 stimulates proliferation of, and immunoglobulin production by, B cells. Moreover, Ztnf4 is a ligand for TACI and is also known in the art as BLyS, neutrokin  $\alpha$ , BAFF, TALL-1 and THANK.

Bram et al. disclose methods of using genetically engineered constructs to regulate B-cell activity through its interaction with cellular receptor ligands. Said constructs can consist of the extracellular domain of the TACI receptor fused to the Fc domain of an immunoglobulin (see page 24, lines 24-26). Moreover, Bram et al. disclose that the "subunits" of the construct (i.e. TACI and the Fc domain of the Ig) can be linked by peptide bonds (see page 20, line 1). Bram et al. further disclose that said extracellular domain has the amino acid sequence corresponding to about residue 1 to about residue 166 of the consensus sequence of TACI and that the ligand binding region is a sub-fragment of the extracellular domain (see page 18, lines 27-30). Said constructs (fusion proteins) intercept the normal endogenous ligands (i.e. ztnf4) that serve to cross-link and activate the TACI proteins on the surface of cells thus inhibiting the ligand's activity (see page 8, lines 1-6). Consequently, by utilizing the methods and materials disclosed by Bram et al., one would necessarily inhibit B cell proliferation, even though its identity is not known since ztnf4 is an **endogenous ligand of TACI**. One does not need to know the identity of the TACI ligand in order to practice the method disclosed by Bram et al. hence Applicant's argument that the identification of the ztnf4 ligand would require undue experimentation is not germane. The instant claims only require that the TACI fusion protein be administered to an individual in order to

Art Unit: 1645

inhibit B cell proliferation and that said composition binds BLyS. Bram et al. disclose the administration of the same the compositions for the expressed purpose of inhibiting B cell proliferation (which is a ztnf4 activity). Moreover, since the fusion proteins disclosed by Bram et al. are identical to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention (including the ability to bind the ztnf4 ligand).

Finally, with regard to the limitation "proteins comprising one or more polypeptide fusions" recited in claims 105-106 and 110-111, Bram et al. anticipates this limitation since their disclosed fusion protein comprise one polypeptide fusion (i.e. the TACI-Fc fusion protein constitutes a single polypeptide fusion).

Bram et al. differs from the claimed invention in that they do not disclose the specific use of 1gG1 heavy chains in fusion proteins.

Presta et al. disclose methods of making fusion proteins comprising the Fc portion of an immunoglobulin (including IgG1)[see column 5, lines 48-55]. Presta et al. further disclose that the Fc portions of the various immunoglobulins have an increased circulatory half-life (see abstract and column 11, lines 63-65). Presta et al. teach that the Fc portions of the various immunoglobulins can be used interchangeably (see column 7, lines 3-45)

It would have been obvious for one of skill in the art at the time of the invention to modify the teachings of Bram et al. to include the teachings of Presta et al. because it is within the skill of the art to modify B cell activity (i.e. reduce B cell proliferation) by administering TACI receptor fusions comprising the Fc portion of an immunoglobulin, and because Presta et al. teach it is within the skill in the art to construct and use fusion proteins comprising the Fc portion of IgG1. One would have been motivated to do so in order to achieve the expected result

Art Unit: 1645

of generating TACI/Fc fusions functional in the methods disclosed by Bram et al. that have the increased circulatory half-life as disclosed by Presta et al.

Based on the state of the art and the teachings of the cited art, and absent of any evidence to the contrary, there would have been a reasonable expectation of success in combining the disclosure of Bram et al. with that of Presta et al. to obtain TACI/IgG1 Fc fusion proteins that are functional in the methods taught by Bram et al.

The rejection of claims 89 and 102-111 under 35 U.S.C. 103(a) as being unpatentable over Bram et al. (U.S. Patent 5,969,102 – IDS-5), as cited above, in view of Presta et al. (U.S. Patent 5,739,277) is maintained for reasons of record.

**Applicant argues:**

1. Bram et al. do not teach the BLyS protein, its activities or the ability of TACI and BLyS to bind (see above).
2. The disclosure by Presta et al. is insufficient to overcome the aforementioned deficiency.
3. Since the combination of references fails to teach all the limitations of the instant invention, their combined teachings does not render the presently claimed invention obvious.

Applicant's arguments have been fully considered and deemed non-persuasive.

Zntf4 is a member of the tumor necrosis factor (TNF) superfamily. Zntf4 stimulates proliferation of, and immunoglobulin production by, B cells. Moreover, Zntf4 is a ligand for TACI and is also known in the art as BLyS, neutrokinine  $\alpha$ , BAFF, TALL-1 and THANK.

Bram et al. disclose methods of using genetically engineered constructs to regulate B-cell activity through its interaction with cellular receptor ligands. Said constructs can consist of the extracellular domain of the TACI receptor fused to the Fc domain of an immunoglobulin (see column 17, lines 16-18). Moreover, Bram et al. disclose that the “subunits” of the construct (i.e. TACI and the Fc domain of the Ig) can be linked by peptide bonds (see column 13, line 64). Bram et al. further disclose that said extracellular domain has the amino acid sequence corresponding to about residue 1 to about residue 166 of the consensus sequence of TACI and that the ligand binding region is a sub-fragment of the extracellular domain (see column 13, lines 7-12). Said constructs (fusion proteins) intercept the normal endogenous ligands (i.e. ztnf4) that serve to cross-link and activate the TACI proteins on the surface of cells thus inhibiting the ligand’s activity (see column 5, lines 45-53). Consequently, by utilizing the methods and materials disclosed by Bram et al., one would necessarily inhibit B cell proliferation, even though its identity is not known since ztnf4 is an **endogenous ligand of TACI**. One does not need to know the identity of the TACI ligand in order to practice the method disclosed by Bram et al. hence Applicant’s argument that the identification of the ztnf4 ligand would require undue experimentation is not germane. The instant claims only require that the TACI fusion protein be administered to an individual in order to inhibit B cell proliferation and that said composition binds BLYS. Bram et al. disclose the administration of the same the compositions for the expressed purpose of inhibiting B cell proliferation (which is a ztnf4 activity). Moreover, since the fusion proteins disclosed by Bram et al. are identical to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention (including the ability to bind the ztnf4 ligand).

Finally, with regard to the limitation “proteins comprising one or more polypeptide fusions” recited in claims 105-106 and 110-111, Bram et al. anticipates this limitation since their disclosed

Art Unit: 1645

fusion protein comprise one polypeptide fusion (i.e. the TACI-Fc fusion protein constitutes a single polypeptide fusion).

Bram et al. differs from the claimed invention in that they do not disclose the specific use of IgG1 heavy chains in fusion proteins.

Presta et al. disclose methods of making fusion proteins comprising the Fc portion of an immunoglobulin (including IgG1)[see column 5, lines 48-55]. Presta et al. further disclose that the Fc portions of the various immunoglobulins have an increased circulatory half-life (see abstract and column 11, lines 63-65). Presta et al. teach that the Fc portions of the various immunoglobulins can be used interchangeably (see column 7, lines 3-45)

It would have been obvious for one of skill in the art at the time of the invention to modify the teachings of Bram et al. to include the teachings of Presta et al. because it is within the skill of the art to modify B cell activity (i.e. reduce B cell proliferation) by administering TACI receptor fusions comprising the Fc portion of an immunoglobulin, and because Presta et al. teach it is within the skill in the art to construct and use fusion proteins comprising the Fc portion of IgG1. One would have been motivated to do so in order to achieve the expected result of generating TACI/Fc fusions functional in the methods disclosed by Bram et al. that have the increased circulatory half-life as disclosed by Presta et al.

Based on the state of the art and the teachings of the cited art, and absent of any evidence to the contrary, there would have been a reasonable expectation of success in combining the disclosure of Bram et al. with that of Presta et al. to obtain TACI/IgG1 Fc fusion proteins that are functional in the methods taught by Bram et al.

*New Grounds of Rejection*

*35 USC § 112*

Claims 89 and 102-111 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a vast genus of **soluble forms of ztnf4 receptors**. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession of the claimed invention. To adequately describe the genus of soluble forms of ztnf4 receptors, Applicant must adequately describe not only what constitutes a soluble ztnf4 receptor but also what constitutes the ztnf4 ligand. However, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of soluble ztnf4 receptors to which the claims are drawn, such as a correlation between the structure of the receptors and its recited function (i.e. inhibiting B-cell proliferation and binding ztnf4), so that the skilled artisan could immediately envision, or recognize at least a substantial number of



Art Unit: 1645

members of the claimed genus. The claims are drawn to the use of any soluble protein comprising a sequence substantially identical to the ztnf4 receptor in a method for inhibiting B lymphocyte proliferation. The specification discloses that three polypeptides, BR43x2, TACI and BCMA are disclosed to be able to bind ztnf4. However, the specification is silent as to which, if any, of these three receptors can inhibit B cell proliferation. The specification does not place any structure, chemical or functional limitations on the variants of ztnf4 receptors. The recitation of " ztnf4 receptor" does not convey a common structure or function. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted (e.g. TACI and BCMA). Moreover, the specification and the claims do not provide any guidance on the structure of the polypeptide and what changes can or cannot be made and retain the recited function. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the function of the binding of ztnf4 alone is insufficient to describe the genus of "soluble ztnf4 receptor" polypeptides of that function equivalently. One of skill in the art would reasonable conclude that the disclosure of three sequences: SEQ ID NO:6 (TACI), SEQ ID NO:8 (BCMA) and SEQ ID NO:4 (BR43x2), fails to provide a representative number of species of soluble ztnf4 receptors to describe the claimed genus.

MPEP § 2163.02 states, “[a]n objective standard for determining compliance with the written description requirement is, ‘does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed’ ”. The courts have decided:

The purpose of the “written description” requirement is broader than to merely explain how to “make and use”; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the “written description” inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

*The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, “Written Description” Requirement* (66 FR 1099-1111, January 5, 2001) state, “[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was ‘ready for patenting’ such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention” (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual

Art Unit: 1645

reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of more than one species within the genus. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of **soluble forms of ztnf4 receptors** is not deemed representative of the genus of polypeptides to which the claims refer.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866.

The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

Art Unit: 1645

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Robert A. Zeman

July 27, 2004